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Concise report

Nailfold capillary abnormalities in erectile dysfunction of systemic sclerosis: a EUSTAR group analysis

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Abstract

Objective. The objective of this study was to analyse an association between nailfold capillary abnormalities and the presence and severity of erectile dysfunction (ED) in men with SSc.

Methods. A cross-sectional analysis of the prospective European League Against Rheumatism (EULAR) Scleroderma Trial and Research database was performed. Men with SSc were included if they had undergone nailfold capillaroscopy and simultaneous ED assessment with the 5-item International Index for Erectile Function (IIEF-5).

Results. Eighty-six men met the inclusion criteria. Eight men (9.3%) had not had sexual intercourse and could not be assigned an IIEF-5 score. Sixty-nine of the 78 men (88.5%) with an IIEF-5 score had nailfold capillary abnormalities, of whom 54 (78.3%) suffered from ED. Nine men (11.5%) had no nailfold capillary abnormalities, of whom six (66.7%) had ED ($P = 0.44$). ED was more frequent in older men ($P = 0.002$) and in men with diffuse disease ($P = 0.06$). Men with abnormal capillaroscopy had a higher median EULAR disease activity than men without ($P = 0.02$), a lower diffusing capacity of the lung ($P = 0.001$) and a higher modified Rodnan skin score ($P = 0.04$), but mean IIEF-5 scores did not differ [15.7 (S.D. 6.2) *vs* 15.7 (S.D. 6.3)]. IIEF-5 scores did not differ between men with early ($n = 12$), active ($n = 27$) or late ($n = 27$) patterns (IIEF-5 scores of 17.9, 16.3 and 14.7, respectively). There were no differences in the prevalence of early, active and late capillaroscopy patterns between men with or without ED.

Conclusion. Neither the presence or absence of abnormal capillaroscopy findings nor the subdivision into early, active and late patterns is associated with coexistent ED in SSc.

Key words: systemic sclerosis, nailfold capillaroscopy, scleroderma pattern, erectile dysfunction, pathogenesis, vasculopathy, ageing.

CLINICAL SCIENCE

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Introduction

Patients with SSc frequently have clinical complications of vascular damage such as RP, digital ulcers, renal crisis, pulmonary arterial hypertension and abnormal nailfold capillaries [1, 2]. After an average of 3 years of disease duration, ~80% of men with SSc also suffer from erectile dysfunction (ED) [3, 4]. The pathogenesis of ED in SSc involves collagen deposition and fibrosis in the corpus cavernosum [5] and therefore clearly differs from the macroangiopathy observed in atherosclerosis. It is unclear, however, if microvascular damage may precede or even parallel the fibrotic changes in penile tissue that ultimately account for ED.

Small vessels can be visualized by nailfold capillaroscopy. In SSc, nailfold findings are typically classified into normal, early, active and late scleroderma patterns [2, 6]. Nailfold abnormalities and patterns derived from them are associated with circulating markers of vascular disease [7], significantly and gradually increase during SSc progression [6] and have been demonstrated to predict future vascular complications, such as severe cutaneous and pulmonary involvement [8–11].

While ED in SSc has already been addressed in a previous paper [4], we aimed to gain insights about a possible contribution of microvascular damage to the ED observed in SSc patients, and therefore we asked if there is a link between nailfold capillary abnormalities and the presence or severity of ED. To address this issue we analysed the database of the European League Against Rheumatism (EULAR) Scleroderma Trial and Research (EUSTAR) group.

Methods

The multinational EUSTAR database was inaugurated in 2004. Participating centres are required to have local ethics committee approval; patients must provide informed written consent prior to entry and fulfil the ACR classification criteria for SSc [12]. For the purpose of this study, the EUSTAR electronic data entry system, which prospectively follows patients in yearly visits, was amended by a separate data form with items specific to the ED study. Men with SSc were included in this analysis if they had undergone nailfold capillaroscopy and were simultaneously administered the 5-item International Index for Erectile Function (IIEF-5) questionnaire, an index of ED severity that is validated in several languages, has high retest reliability and is sensitive and specific for detecting treatment-related changes [13]. The IIEF-5 provides a numerical score that is classified into five categories of ED severity: severe (score 5–7), moderate (score 8–11), mild to moderate (score 12–16), mild (score 17–21) and no ED (score 22–25) [13]. Nailfold findings were analysed on eight fingers and the pathologies were classified into normal, early, active or late scleroderma patterns [6]. In case of multiple annual datasets, we analysed the last visit.

Statistical analysis was carried out using Stata (version 11.2; StataCorp, College Station, TX, USA) by analysing SSc presentations for associations between ED, nailfold capillary abnormalities and other clinical features of ED. The dataset was analysed using chi-square and Fisher's tests, *t*-tests, analysis of variance (ANOVA), Wilcoxon and Kruskal–Wallis tests, as appropriate. Continuous data are presented as mean (S.D.) or median with interquartile range (IQR), as appropriate, while binary parameters are presented as percentages.

Results

Eighty-six men had undergone nailfold capillaroscopy and were simultaneously administered the IIEF-5 questionnaire and therefore met the inclusion criteria. Of these, eight men (9.3%) had not had sexual intercourse in the last 6 months and could therefore not be assigned an IIEF-5 score. These were excluded from the analysis. In three men with abnormal capillaroscopy, the exact pattern (early, active or late) was not specified.

We first analysed SSc disease characteristics according to the presence or absence of ED and additionally by categorizing men by ED severity (Table 1). Although more patients suffering from ED had a late scleroderma pattern (47.1%) than patients without ED (20%, $P = 0.06$), there was no difference in the prevalence of a late scleroderma pattern between men with mild and severe ED. Furthermore, the early and active patterns of nailfold capillary abnormalities were even less frequent in SSc men with ED compared with those without ED (Table 1). With respect to other vascular complications of SSc, there was no association of ED with the presence of digital ulcers and no significant association with signs of pulmonary arterial hypertension. It should be noted, however, that none of the 18 men without ED had a pulmonary arterial systolic pressure $\geqslant 40$ mmHg, as estimated by echocardiography. ED was associated with age ($P = 0.002$) and marginally associated with skin involvement in terms of diffuse disease ($P = 0.06$) at univariate analysis. A multivariate analysis confirmed the association of ED with age, but failed to detect an association with nailfold patterns. Numerically, more patients with diffuse disease had severe ED and more patients with Scl70 also had severe ED. However, we did not find a significant association between these parameters and the presence or absence of ED ($P = 0.06$ and 0.59, respectively).

We also analysed our data by grouping patients according to the presence or absence of nailfold capillary abnormalities. Sixty-nine men (88.5%) had nailfold capillary abnormalities, among whom 54 (78.3%) suffered from ED. Only nine patients had no nailfold capillary abnormalities, as expected for an SSc population. The proportion of ED was similar, however, in men without capillary abnormalities (66.7%) in comparison with those with abnormal capillaries (78.3%, $P = 0.44$). Furthermore, the mean IIEF-5 score for men with and without any nailfold capillary abnormality did not differ [15.7 (S.D. 6.2) *vs* 15.7 (S.D. 6.3)]. There was also a trend without significance ($P = 0.31$) in the IIEF-5 scores for men with an early ($n = 12$), active ($n = 27$) or late ($n = 27$) pattern (IIEF-5 scores of 17.9, 16.3 and 14.7, respectively).

Table 1 Comparison of SSc patients with and without ED

	No ED ($n = 18$)	ED mild ($n = 22$)	ED mild to moderate ($n = 19$)	ED moderate ($n = 8$)	ED severe ($n = 11$)	Any ED ($n = 60$)	*P*-value, any ED *vs* no ED*
Age, mean (S.D.), years	43.3 (14.8)	52.7 (8.9)	55.8 (12.7)	53.1 (6.4)	48.0 (6.7)	52.9 (9.9)	0.002**
SSc duration by RP, median (IQR), years	7.1 (4.8–15.7)	9.6 (3.8–13.4)	4.4 (3.7–9.5)	11.5 (3.1–19.3)	5.7 (1.2–13.5)	6.1 (3.2–13.4)	0.64
SSc duration by first non-RP symptom, median (IQR), years	6.2 (4.0–8.7)	6.0 (3.0–18.5)	3.8 (1.5–5.3)	11.3 (3.5–18.9)	5.4 (1.9–9.8)	5.0 (2.2–11.3)	0.61
Duration of ED, median (IQR), years	—	1.6 (0.3–4.4)	1.0 (0.4–2.7)	1.0 (0.8–6.1)	1.3 (0.1–7.5)	1.2 (0.4–3.8)	N/A
Diffuse SSc, *n* (%)	4 (22.2)	9 (40.9)	11 (57.9)	3 (37.5)	7 (63.6)	30 (50.0)	0.06
EULAR SSc activity score, median (IQR)	1.25 (0.5–3.0)	0.5 (0.5–2.0)	2.25 (0.75–4.0)	0.5 (0.5–1.0)	1.75 (0.5–3.0)	1 (0.5–2.5)	0.75
Scl70 autoantibody positive, *n* (%)	6 (33.3)	5 (23.8)	7 (38.9)	4 (57.1)	7 (63.6)	23 (40.4)	0.59
mRSS, median (IQR)	8 (5–15)	9 (2–19)	11 (8–17)	12 (9–15)	13.5 (7–20)	11 (7–18)	0.19
PAPsys $>$ 40 mmHg, *n* (%)	0	5 (26.3)	1 (6.3)	0	2 (20.0)	8 (15.4)	0.19
FVC, median (IQR), % of normal	91.5 (85–99)	96 (87–109)	95.5 (87–100)	99 (76–111.5)	85 (56–100)	94.5 (84–103)	0.85
Digital ulcers, *n* (%)	8 (44.4)	7 (31.8)	13 (68.4)	3 (37.5)	5 (45.5)	28 (46.7)	0.87
Naifold capillaroscopy normal, *n* (%)	3 (16.7)	3 (13.6)	2 (10.5)	0	1 (9.1)	6 (10.0)	0.44
Nailfold capillaroscopy not normal, *n* (%)	15 (83.3)	19 (86.4)	17 (89.5)	8 (100.0)	10 (90.9)	54 (90.0)	0.44
Early scleroderma pattern, *n* (%)	3 (20.0)	5 (26.3)	2 (12.5)	2 (28.6)	0	9 (17.7)	0.84
Active scleroderma pattern, *n* (%)	9 (60.0)	4 (21.1)	8 (50.0)	2 (28.6)	4 (44.4)	18 (35.3)	0.09
Late scleroderma pattern, *n* (%)	3 (20.0)	10 (52.6)	6 (37.5)	3 (42.7)	5 (55.6)	24 (47.1)	0.06

ED: erectile dysfunction; EULAR: European League Against Rheumatism; IQR: interquartile range; mRSS: modified Rodnan skin score; PAPsys: systolic pulmonary arterial pressure (estimated by echocardiography); FVC: forced vital capacity. *Analysed by chi-square tests for categorical data or *t*-tests or Wilcoxon test for continuous data. **P-value $\leqslant 0.05$ was considered statistically significant.

Nevertheless, and as determined previously [7], capillaroscopy abnormalities were associated with a higher median EULAR DAS ($P = 0.02$), a lower diffusion capacity of the lung for carbon monoxide (DLCO) ($P = 0.001$), a lower forced vital capacity ($P = 0.04$) and a higher modified Rodnan skin score (mRSS, $P = 0.04$).

Discussion

The main finding of our analysis is that nailfold capillaroscopy lacks a clinically useful association with the presence and severity of ED in SSc. Erection is a neurovascular phenomenon under hormonal control. The mechanisms of erection in healthy men include arterial dilatation, smooth muscle relaxation and activation of the corporeal veno-occlusive mechanism [5]. Although our data are unable to exclude completely a true vascular mechanism in the onset of SSc-associated ED, they do not support involvement of a generalized small vessel disease in penile fibrosis and point towards the possibility of veno-occlusive dysfunction or other mechanisms of ED [14, 15]. The lack of association between diffuse disease, Scl70 autoantibody positivity and the presence of ED has also been shown before in a different subset of EUSTAR study group men [4]. This finding suggests that ED may not be linked to the overall severity of SSc.

As in any cross-sectional analysis, we cannot exclude recruitment or ascertainment bias, although a previous analysis demonstrated good intercentre reliability of nailfold capillaroscopy [16]. The IIEF-5 score does and cannot evaluate men without intercourse and additional data on impotence were not addressed in this analysis. The lack of knowledge about the exact reasons for sexual abstinence in the eight men that were excluded from our analysis due to the lack of intercourse raises the possibility of a bias. We have therefore also tested whether these eight men would have altered our conclusions if they were attributed to the group with severe ED. In this analysis (not shown), there was still no significant association between ED and capillaroscopy patterns, making this form of bias unlikely.

The fact that our dataset was able to replicate known associations between capillaroscopy abnormalities and pulmonary and cutaneous SSc complications [9–11] suggests that the statistical power of our analysis was adequate. The number of analysed male SSc patients in this study is similar or even exceeds the number of populations found to be predictive of future organ manifestations in other capillaroscopy studies [8, 9, 11, 17]. Despite the fact that a dynamic transition of microvascular damage through different neurovascular compression patterns has been demonstrated [18], the classification of capillaroscopy findings into early, active and late patterns may lack sensitivity in detecting and distinguishing smaller degrees of vascular involvement. Therefore this study should be replicated using quantitative scores [19]. Capillaroscopy predominantly evaluates structural impairment, thus further techniques that are able to evaluate microvascular function, such as laser Doppler imaging, might be helpful to clarify these questions.

Taken together, although nailfold capillaroscopy is associated with some vascular organ complications, such as digital ulcers, pulmonary arterial hypertension and skin involvement [7–9], it appears that neither the presence or absence of abnormal capillaroscopy findings nor the subdivision into early, active and late patterns is a useful tool in predicting coexistent ED.

Rheumatology key messages

- Nailfold capillary abnormalities in men with SSc are associated with SSc organ complications.
- There is no association between abnormal capillaroscopy patterns and the presence or severity of erectile dysfunction in men with SSc.

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